Remarks

I. Status of the Claims

Reconsideration of this application is respectfully requested.

By the foregoing amendment, claim 5 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. This amendment is sought to place the claims into condition for allowance or for consideration on appeal, and introduce no new matter. Entry and consideration of this amendment are respectfully requested.

Upon entry of this amendment, claims 31-66 are pending in the application, with claims 31, 44, and 57 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated March 14, 2006, the Examiner has made two rejections of the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. The Enablement Rejection Under 35 U.S.C. § 112, First Paragraph is Traversed

At pages 3-5 of the Office Action, claims 31-33, 35-46 and 48-66 have been rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly would not be enabling for molecules of limited homology to the disclosed sequence. Applicants respectfully traverse this rejection.

According to the Examiner:

> Applicant hasn't taught what is required for that particular activity; i.e. we don't know what we could change and what we could not for that particular activity. . . . . Applicant needs to provide the guidance as to how we are able to predict which ones will work.

Office Action at page 4-5. Applicants respectfully disagree. Applicants submit that the claims are fully enabled by the specification. In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the claimed invention must be enabled so that a person of skill in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Some experimentation, even a considerable amount, is not "undue" if, *e.g.*, it is merely routine. . . . *Id.* In addition, an Applicant is not limited to the confines of the specification to provide the necessary information to enable an invention. *See In re Howarth*, 654 F.2d 103, 105-6, 210 USPQ 689, 692 (CCPA 1981). An Applicant need not supply information that is well known in the art. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *Howarth*, 654 F.2d at 105-6, 210 USPQ at 692; *see also In re Brebner*, 455 F.2d 1402, 173 USPQ 169 (CCPA 1972) (finding a disclosure enabling because the procedure for making the starting material, although not disclosed, would have been known to one of ordinary skill in the art as evidenced by a Canadian patent). Applicants assert that it would require no more than routine experimentation for a skilled artisan to practice the full scope of the claimed invention in view of the teachings in the specification and the knowledge

available in the art. Thus, the enablement requirement of 35 USC § 112, first paragraph, is fully satisfied for claims 31-33, 35-46 and 48-66.

Claims 31-33, 35-46 and 48-66 are presently directed to a polynucleotide comprising a nucleic acid which encodes a polypeptide 80%-95% identical to a polypeptide comprising amino acids 1-310 or 31-310 of SEQ ID NO:2, wherein the polypeptide modulates inhibition of axonal elongation, as well as vectors and host cells that comprise the polynucleotide.

A person of ordinary skill in the art, based on the specification and the teachings generally available in the art, would be able to make and use the full scope of the claimed invention. First, a person of ordinary skill in the art would be able to generate a DNA molecule that encodes a polypeptide comprising amino acids 1-310 or 31-310 of SEQ ID NO:2 or a polypeptide, which is at least 80%-95% homologous thereto. The specification provides methods for obtaining DNA molecules which encode polypeptides that are at least 80%-95% homologous to amino acids 1-310 or 31-310 of SEQ ID NO:2; such methods involving site-directed mutagenesis, PCR-mediated mutagenesis and saturation mutagenesis. *See* specification at page 58, lines 24-27.

Once obtained, DNA molecules that encode polypeptides that are at least 80%-95% homologous to amino acids 1-310 or 31-310 of SEQ ID NO:2 can easily be tested for the ability to modulate inhibition of axonal elongation using routine techniques. *See, e.g.*, Huang *et al.*, *Neuron 24*:639-47 (1999). Additionally, in the present specification, Applicants teach assays that could be routinely used by one of ordinary skill in the art to test whether variants had the required function. For example, binding assays could easily be performed to determine whether a given polypeptide of

the invention can modulate inhibition of axonal elongation by binding to a ligand of NgR2. *See* specification at page 69, line 25 through page 76, line 2. Thus, the full range of DNA molecules encompassed by claims 31-33, 35-46 and 48-66, can be made and analyzed by persons of ordinary skill in the art using only routine methods and experimentation.

The Examiner, in explaining the rejection, has emphasized that the Applicants are required to "teach what can be changed and what can not be changed in a polypeptide . . . to preserve its functional activity." *See* Office Action at page 5. In addition, the Examiner emphasized that Kobe *et al.* does not teach what can be changed and what can not be changed because

> Although Kobe et al. teach that the common structure of the consensus residues of leucine-rich repeats . . ., Kobe et al. also disclose that the function of these proteins is mostly due to the specific compositions of non-consensus residues within the proteins and is also influenced by the length of the repeats and the flanking domains.

See Office Action at page 5. While the Examiner is correct that the relationship between the sequence of a protein and its biological function may in fact be complex, and it may be difficult to predict the exact functional consequences of a particular mutation, Applicants respectfully point out that in order to practice the claimed invention, a skilled artisan would not need to be able to predict the structural and/or functional consequences of particular mutations or base changes. To practice the full scope of the claimed invention, the skilled artisan would only need to be able to: (a) obtain DNA molecules that encode polypeptides that are at least 80%-95% homologous to amino acids 1-310 or 31-310 of SEQ ID NO:2, and (b) test them for the ability to modulate inhibition of axonal elongation. As discussed above, both of these processes would be routine in the

art. Admittedly, these processes may result in the production of DNA molecules that encode proteins that are at least 80%-95% homologous to amino acids 1-310 or 31-310 of SEQ ID NO:2 but that *do not* modulate inhibition of axonal elongation. The skilled artisan, however, would be able to easily identify and discard such non-active molecules that do not fall within the scope of the claimed invention. Screening for molecules that possess a particular activity is common in the biological arts. Experimentation, even complex experimentation, is not undue if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *see also Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Thus, the uncertainty that may be associated with predicting protein function from sequence data is of little relevance in an analysis of the enablement of Applicants' claims. A skilled artisan would be expected to engage in screening for DNA molecules that encode polypeptides that are at least 80%-95% homologous to amino acids 1-310 or 31-310 of SEQ ID NO:2 and that modulate inhibition of axonal elongation. Such screening, even if it resulted in the identification of molecule not having the desired activity, would be considered routine in the art.

In view of the forgoing discussion, Applicants submit that a person having ordinary skill in the art, in view of the teachings of the specification, would be able to make and practice the full scope of Applicants' claimed invention. In addition, Applicants contend that the Examiner has failed to provide acceptable objective evidence or sound scientific reasoning that shows that it would require undue experimentation for a

skilled artisan to make and use the claimed invention, and therefore has failed to establish a *prima facie* case of non-enablement. Accordingly, Applicants respectfully request that the rejection of claims 31-33, 35-46 and 48-66 under 35 USC § 112, first paragraph, be reconsidered and withdrawn.

IV. The Written Description Rejection Under 35 U.S.C. § 112, First Paragraph is Traversed

At pages 6-7 of the Office Action, claims 31-33, 35-46 and 48-66 have been rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to meet the written description requirement. Applicants respectfully traverse this rejection. According to the Examiner,

> the claims are drawn to polynucleotides and a method of making polypeptides, which encompass variants and sequences comprising fragments that could vary widely in structure and function. Since there is no guidance as to what could be changed and what could not be changed to preserve any common characteristics, . . . the structural/functional features of these polypeptides are unpredictable. In addition, Applicant is not in possession of all polynucleotides comprising a polynucleotide encoding for at least 80% identity of the polypeptide of amino acids 1-310 of SEQ ID NO:2, which includes unknown sequences.

Office Action at page 6. Applicants respectfully disagree. Applicants submit that the specification describes the presently claimed invention in sufficient detail such that one skilled in the art would reasonably conclude that Applicants had possession of the claimed invention as of the effective filing date. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Although the structure of a protein is important for its biological function, the written description requirement may

nonetheless be satisfied for a claim to a genus of DNA molecules that are at least 80%-95% homologous to a disclosed nucleotide sequence. This proposition is specifically supported by the USPTO's Synopsis of Application of Written Description Guidelines (hereinafter "Written Description Synopsis").

Example 14 of the Written Description Synopsis involves an analysis of the following claim: "A protein having[1] SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B." The specification supporting this claim provides the following information:

> The specification exemplifies a protein isolated from liver that catalyzes the reaction of A→B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

See Written Description Synopsis, Example 14.

The Written Description Synopsis, Example 14, concludes that the disclosure meets the requirements of 35 USC § 112, first paragraph, in part because "procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art." *See id.* Moreover, it is noted that:

> [t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence

[1] "[H]aving" is well accepted to be open-ended in the same way "comprising" is. *See, e.g., Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1573, 43 USPQ2d 1398, 1410 (Fed. Cir. 1997) (In the context of a cDNA having a sequence coding for human PI, the term "having" still permitted inclusion of other moieties.).

> of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

See Written Description Synopsis, Example 14.

The situation presented in Example 14 of the Written Description Synopsis closely parallels the circumstances surrounding Applicants' claims and the written description provided therefor. As such, Applicants submit that the guidance and instructions provided by the USPTO for analyzing a claim for compliance with the written description requirement mandates that the written description requirement of § 112, first paragraph, is satisfied for Applicants' claims.

First, in Example 14 of the Synopsis, it is stated that "all variants [encompassed by the claim] must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO:3." Similarly, all of the species of the polynucleotides encompassed by Applicants' claims must encode polypeptides that have at least 80%-95% homology to amino acids 1-310 or 31-310 of SEQ ID NO:2 and these polypeptides must modulate inhibition of axonal elongation.

Second, it is noted in Example 14 that "[t]here is a single species disclosed, that species being SEQ ID NO:3;" and that "[t]here is actual reduction to practice of the single disclosed species." Likewise, Applicants have disclosed SEQ ID NO:2 in the specification and have shown actual reduction to practice of at least one molecule, *e.g.*, SEQ ID NO:2. *See* specification at Table 5 and Example 2.

Third, according to Example 14, "procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional

in the art." Likewise, procedures for making polynucleotides which encode polypeptides which are at least 80%-95% homologous to amino acids 1-310 or 31-310 of SEQ ID NO:2 and which modulate inhibition of axonal elongation are conventional in the art. As stated in the specification:

> [m]utations can be introduced . . . by standard techniques, *e.g.*, site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acids substitutions can be made at one or more amino acid residues predicted to be non-essential. Alternatively, mutations can be introduced randomly along a NgR coding sequence. This can be accomplished, *e.g.*, by saturation mutagenesis.

See specification at page 58, lines 22-27. Applicants note that these methods were well known to persons having ordinary skill in the art at the time of the invention. In addition, the proteins can easily be tested for modulation of axonal elongation using the procedures described in the specification (*see* discussion immediately below) as well as with other methods that are conventional in the art for testing the biological activity of a protein.

Fourth, in Example 14 of the Written Description Synopsis, it is stated that "an assay is described [in the specification] which will identify other proteins having the claimed catalytic activity." Correspondingly, in Applicants' specification, assays are described which will identify other proteins having the required activity. For example, Applicant teaches assays that could be routinely used by one of ordinary skill in the art to test whether variants had the required function. For example, binding assays could easily be performed to determine whether a given polypeptide of the invention can modulate inhibition of axonal elongation by binding to a ligand of NgR2. *See* specification at page 69, line 25 through page 76, line 2. In addition, DNA molecules that encode

polypeptides comprising amino acid sequences that are at least 80%-95% homologous to amino acids 1-310 or 31-310 of SEQ ID NO:2 can easily be tested for the ability to modulate inhibition of axonal elongation using routine techniques. *See, e.g.*, Huang *et al.*, *Neuron 24*:639-47 (1999).

As demonstrated above, the hypothetical situation described in Example 14 of the USPTO's Written Description Synopsis is very similar to the situation presented for Applicants' claims. Since it is concluded that adequate written description is provided for the hypothetical claim in Example 14, it follows that there is adequate written description for Applicants' claims.

Applicants' contention that the written description requirement is satisfied for the present claims is not only supported by the USPTO's Written Description Synopsis, but also by the Federal Circuit's interpretation and application of 35 USC § 112, first paragraph. *See, e.g.*, *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). According to the Federal Circuit, the disclosure of a patent must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. *See id.* at 1568, 43 USPQ2d at 1406. Applicants have provided in the specification a detailed analysis of the sequence characteristics of the amino acid sequence of SEQ ID NO:2. *See* specification at page 57, line 14, through page 58, line 10. Applicants have also described various activities possessed by the polypeptides and methods for assaying such activities. *See, e.g.*, specification at page 12, lines 26-28 and page 58, lines 27-31. Moreover, methods for making DNA molecules that encode polypeptides that are 80%-95% homologous to a reference polypeptide are common in the field of molecular biology and are also described in the specification.

See, e.g., specification at page 58, lines 22-27. In view of these factors, a skilled artisan would be able to clearly visualize and recognize the DNA molecules encompassed by the present claims.

Therefore, based on Federal Circuit precedent and the guidance provided by the USPTO, Applicants submit that there is adequate written description for claims 31-33, 35-46 and 48-66. Accordingly, Applicants respectfully request that the rejection of claims 31-33, 35-46 and 48-66 under 35 USC § 112, first paragraph, for insufficient written description, be reconsidered and withdrawn.

V. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Shannon A. Carroll

Shannon A. Carroll, Ph.D.
Attorney for Applicants
Registration No. 58,240

Date: May 4, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

521475_1.DOC